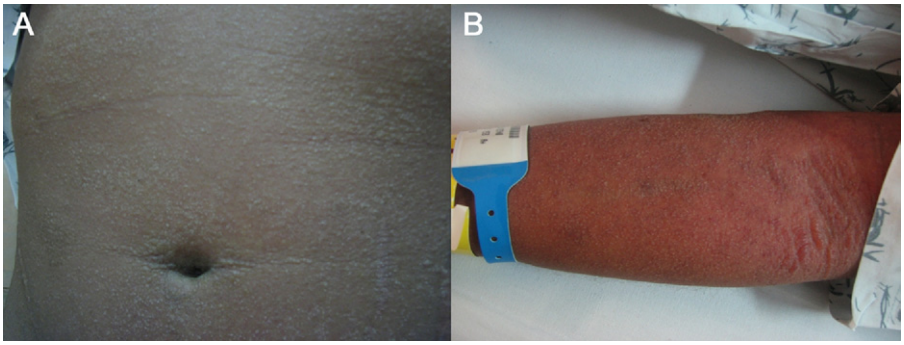

Figure 1. Multiple erythematous pustular eruptions involving the trunk (A) and upper extremities (B).

an elevated C-reactive protein concentration (11.23 mg/dL). All other laboratory values were unremarkable. A biopsy specimen was not taken. The patient was treated with 0.05% topical desonide lotion for the rash, the antihistamines hydroxyzine and levocetirizine for the pruritus, and empirical antibiotics for possible systemic infection. On day 4, his fever had subsided completely and all blood culture results were negative. On day 6, generalized cutaneous desquamation occurred with marked resolution of his erythema and pustules.

AGEP is characterized by a sudden onset of fever and widespread numerous nonfollicular sterile pustules and has a benign, self-limiting course.[1] Although most cases of AGEP (>90%) have been associated with drugs, in particular antibiotics, its origin is variable, and it may be triggered by viral infection, hypersensitivity to mercury, or spider bites. Several case reports have described patients with AGEP induced by contrast media, including 2 patients with delayed, generalized, and protracted cutaneous reactions compatible with AGEP after contrast medium administration,[4] 1 patient with contrast-induced AGEP,[5] and 1 patient who developed a pruritic pustular eruption on 2 separate occasions after administration of a nonionic contrast medium.[6]

The main histopathologic findings in most patients with AGEP include spongiform superficial pustules, papillary edema, polymorphonuclear cells with some perivascular eosinophils, and leukocytoclastic vasculitis with fibrinoid deposits. Our patient had the characteristic morphologic features and course of AGEP, except that histologic features could not be identified because no biopsy specimen was obtained.

To our knowledge, this is the first case of AGEP induced by contrast media ever reported in Korea. Physicians should bear in mind that AGEP can be induced by radiocontrast media.

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THE SAFETY AND INTERPRETABILITY OF SKIN TESTS WITH OMALIZUMAB

Omalizumab is an anti-IgE antibody used to reduce exacerbations in patients with moderate to severe allergic asthma. There have been reports of systemic reactions after injection with omalizumab consistent with anaphylactic reactions; however, it remains unclear whether these reactions are caused by IgE sensitization to omalizumab or its excipients vs an alternative non–IgE-mediated mechanism.[1] The product, omalizumab (Xolair; Genentech/Novartis, San Francisco, California) includes the omalizumab antibody and the following excipients: sucrose, L-histidine, L-histidine hydrochloride monohydrate, and polysorbate 20.

To advance our understanding of the potential role of IgE antibodies to omalizumab (or one of its excipients) relative to these reactions, an interpretable result on a skin test to omalizumab and its vehicle is needed. A study to examine whether omalizumab skin testing is safe and to establish an appropriate nonirritating concentration for prick and intradermal testing was conducted. This protocol, the informed consent form, and relevant supporting information were submitted to the Mid* Land Institutional Review Board (Overland, Kansas) by the principal investigator for review and approval before the study was initiated.

Disclosures: Dr Lieberman is a consultant for Genentech Inc. Drs Rahmaoui and Wong are employees of Genentech Inc.

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Table 1. Summary of Reactions to the Intradermal Test in Healthy Volunteers (First Cohort, n = 30) and Allergic Asthma Patients (Second Cohort, n = 30)

Type and reaction	Participants, No. (%)
1:1,000 Dilution[a] (Reconstituted With SW) in 27 Healthy Volunteers	
Excipient	
Positive	6 (22.2)
Negative	21 (77.8)
Omalizumab	
Positive	2 (7.4)
Negative	25 (92.6)
1:100 Dilution[b] (Reconstituted With SW) in 21 Healthy Volunteers	
Excipient	
Positive	7 (33.3)
Negative	14 (66.7)
Omalizumab	
Positive	6 (28.6)
Negative	15 (71.4)
1:10 Dilution (Reconstituted With SW) in 13 Healthy Volunteers	
Excipient	
Positive	0 (0)
Negative	13 (100.0)
Omalizumab	
Positive	0 (0)
Negative	13 (100.0)
1:100,000 Dilution (Reconstituted With NS) in 30 Allergic Asthma Patients	
Excipient	
Positive	1 (3.3)
Negative	29 (96.7)
Omalizumab	
Positive	0 (0)
Negative	30 (100.0)
1:10,000 Dilution[c] (Reconstituted With NS) in 29 Allergic Asthma Patients	
Excipient	
Positive	4 (13.8)
Negative	25 (86.2)
Omalizumab	
Positive	7 (24.1)
Negative	22 (75.9)

Abbreviations: SW, sterile water; NS, normal saline.
[a] For 1:1,000, 4 study participants reacted to excipient only, none reacted to omalizumab only, and 2 reacted to both.
[b] For 1:100, 2 study participants reacted to excipient only, 1 reacted to omalizumab only, and 5 reacted to both.
[c] For 1:10,000, 1 study participant reacted to excipient only, 4 reacted to omalizumab only, and 3 to both.

Two cohorts were recruited into the study, all without previous exposure to omalizumab or other biologic therapies. For safety, initially 30 healthy individuals were skin tested. This was followed by testing 30 patients with allergic asthma. All study participants were tested with a positive control (histamine), a negative control (saline), and sequentially increasing concentrations of omalizumab and placebo omalizumab (vehicle with excipients without omalizumab). Both initial skin prick tests followed by intradermal tests were administered. A positive reaction was defined as a 3-mm wheal or larger and/or a 10-mm or larger erythema over the negative control. A positive test result necessitated stopping the escalation to the next dilution of omalizumab or its vehicle for that individual. In addition, serum samples were assayed for antiomalizumab IgG 10 weeks after skin testing to determine whether testing induced a measurable immune response. The concentrations and results of intradermal tests are summarized in Table 1.

In the first cohort of 30 healthy individuals, irritant wheals to the excipient were noted in 3 individuals at some prick (1 individual reacted to 1:10 and 2 individuals reacted to the undiluted concentration) and many intradermal testing sites. On the basis of the pattern of reactions, it was concluded that the sterile water in which lyophilized omalizumab was reconstituted contributed to the reactions and that for some patients intradermal testing with concentrations greater than 1:1,000 of subcutaneous injectable omalizumab were irritating. Therefore, subsequent dilutions for skin testing were formulated using normal saline (rather than sterile water) and lower concentrations of omalizumab and the placebo vehicle.

In the second cohort, composed of 30 allergic asthma patients, none reacted to skin prick tests using the saline-formulated preparation. When tested intradermally to the saline-formulated preparation, 1 patient reacted to a 1:100,000 concentration of excipient (vehicle), 4 patients reacted to the 1:10,000 concentration of excipient (3 of whom also reacted to omalizumab), and 7 reacted to the 1:10,000 concentration of omalizumab. We used these initial concentrations because there is sufficient protein within these concentrations (a 1:10,000 concentration contains 12.5 μg/mL of protein) to normally produce a positive skin test result. In addition, these types of concentrations have been validated by previous studies of immediate hypersensitivity reactions to monoclonal antibodies.[2] We chose this range of dilutions because a 1:10,000 dilution of omalizumab contains 12.5 μg/mL of protein—a concentration normally sufficient to produce a positive skin test result. The observation that 1 patient at both the 1:10,000 and 1:100,000 dilutions reacted to intradermal injection of excipient without reacting to omalizumab may be explained by the excipient being more irritating in the absence of the monoclonal antibody protein.

There were no unexpected adverse reactions to the skin testing procedure with either omalizumab or its excipients. The concentrations of omalizumab and its excipients used in this study of skin prick and intradermal tests did not elicit an IgG antibody response to omalizumab in the serum samples of patients tested 10 weeks after completion of skin testing.

Thus, skin testing to omalizumab and placebo appears to be safe in patients with allergic asthma. Future studies will be required to determine the safety of testing in patients with reported hypersensitivity reactions to omalizumab.

Skin prick testing with all concentrations diluted with normal saline did not elicit any nonspecific reactions. A 1:100,000 solution of omalizumab, which would be a concentration of 1.25 μg/mL, also did not produce any nonspecific irritant reactions.

This study establishes the methods and concentrations under which skin testing to omalizumab could potentially be used to detect patients with antiomalizumab IgE or the excipients contained in the vehicle use for its administration.

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CODIAGNOSIS OF ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS AND SARCOID IN A SEVERE ASTHMATIC PATIENT

Allergic bronchopulmonary aspergillosis (ABPA) is a respiratory disease that can occur in patients with cystic fibrosis and asthma, resulting in increased morbidity.[1] ABPA is characterized by mucoid impaction and inflammation, which can lead to bronchiectasis, fibrosis, and progressive lung function decline.[1] The classic computed tomography findings of late-stage ABPA are central bronchiectasis with upper lobe predominance. Peripheral nodules and ground glass opacities can also be found earlier, but mediastinal lymphadenopathy is rare.

Sarcoid is a disease often described as the "great imitator." Patients with sarcoidosis present with vague symptoms of fatigue, shortness of breath, cough, night sweats, and occasionally rashes.[2] On computed tomograms, sarcoid classically shows bilateral hilar adenopathy and reticular opacities, and diagnosis is made by the finding of noncaseating granulomas on biopsy.[2] Other common causes of mediastinal and hilar lymphadenopathy include infection, neoplasm, granulomatous disease, and reactive hyperplasia. We describe a case study of severe persistent asthma presenting with bronchiectasis and mediastinal and hilar lymphadenopathy with a diagnosis consistent with ABPA and sarcoidosis.

We present a case of a 38-year-old man with a 3-year history of allergic rhinitis, sinusitis, and severe persistent asthma. In the previous 18 months, he had received 2 courses of systemic corticosteroids and had been treated for pneumonia in the past. His medications included fluticasone propionate and salmeterol (250/50 μg) and montelukast. He noted nocturnal symptoms occurring 2 to 3 times per week and use of albuterol inhaler 2 to 3 times per week. Family history was significant for a father and 2 brothers with severe sinus disease. He owned a landscaping business. The patient had a 5-pack-year smoking history, although he had quit 4 years ago. The results of the physical examination were unremarkable.

Pulmonary function testing showed obstruction with a forced expiratory volume in 1 second (FEV_1) of 2.54 L or 63% of predicted and a FEV_1/forced vital capacity (FVC) ratio of 57% of predicted. Diffusion capacity was normal. Allergy skin prick testing revealed positive reactions to cottonwood tree, ragweed, cat dander, and *Aspergillus fumigatus*. Laboratory testing demonstrated an elevated absolute peripheral blood eosinophil count (0.9 g/μL) and elevated serum IgE level (451 kU/L), which was drawn off systemic corticosteroids. A serum angiotensin-converting enzyme level was not obtained. The results of precipitating serum antibody tests were negative. High-resolution computed tomography demonstrated central bronchiectasis with mucoid impaction suggestive of ABPA and mediastinal lymphadenopathy with the largest lymph node measuring 1.3 × 2.1 cm (Figure 1A). The patient was diagnosed as having asthma complicated by ABPA. Treatment included an extended course of systemic corticosteroids (slowly tapered during 3 months) and increased inhaled corticosteroid dosing. Treatment with omalizumab was also initiated.[3] However, because of the finding of mediastinal adenopathy, which is not common in ABPA, the patient was referred for a video-assisted thoracoscopy. The biopsy results showed noncaseating granulomas, consistent with the diagnosis of sarcoid (Figure 1B). Culture of lung tissue was negative for infection. The results of ophthalmologic examination and 24-hour urinanalysis for calcium were normal. At 1-year follow-up, he reported improvement in symptoms with objective improvement in pulmonary function testing with an FVC of 5.31 L (108% predicted), an FEV_1 of 4.31 L (108% predicted), an FEV_1/FVC ratio of 0.75 with omalizumab, fluticasone propionate–salmeterol (500/50 μg), montelukast, nasal irrigations, mometasone nasal spray, and cetirizine.

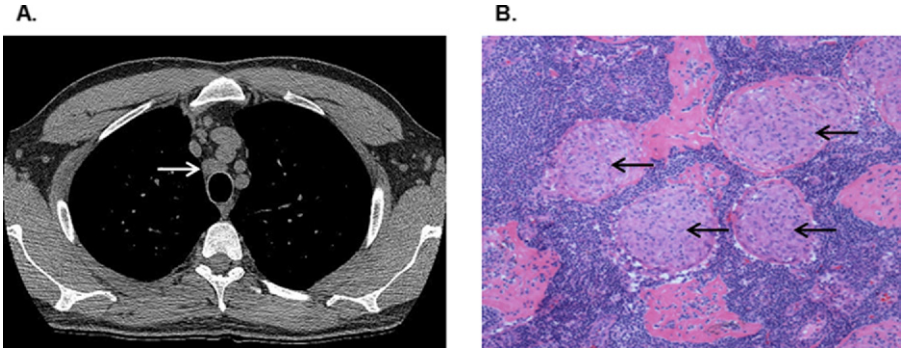

Figure 1. Mediastinal lymph node. A, High-resolution computed tomogram of mediastinal lymph node enlargement measuring 1.3 × 2.1 cm. B, Histologic analysis (hematoxylin-eosin) of mediastinal lymph node (fourth lymph node, right) shows nonnecrotizing (noncaseating) granulomatous inflammation composed of small, tight, "naked" granulomas (arrows), consistent with sarcoid.